physiological art is unpredictable, and that the disclosure in the specification is insufficient to support the breadth of the claims. This rejection is traversed for the following reasons.

It is the Examiner's position that "[t]he claims are drawn to using genomic markers to determine the stage of organ development, the gene expression in various stages of the development in different organs are bound to be distinct among different classes of vertebrate, the specification fails to teach which of genes expressed at what stage in which organ of the which vertebrate could be used as a determining factor for amphibians, birds, bony fish, chimaera chondrichthian, mammal, reptile, etc., one skilled in the art could not practice the claimed invention without first carrying out extensive experimentation to determine the parameters for practice the invention, i.e. which genome DNA could be used for stage markers for a particular organ in a particular vertebrate animal." The specification of the present invention describes, "For examination of the cell differentiation or the stages, it is preferable to conduct quantitative analysis using many kinds of gene markers or antibodies simultaneously with observation of the tissues" (page 7, lines 15-18), and clearly states that the stage of organ development can be determined by observation of tissues as well, and that "first carrying out extensive experimentation to determine the parameters using DNA as stage markers for practice of the invention" is not always needed. Further, the specification of the present invention also describes, "More defined testing can be performed by using genome DNA, which expresses corresponding to the stage of *in vitro* induced organ, as a molecular marker." (page 8, lines 5-7), but "**primary response gene**" and "**secondary response gene**", which could be molecular markers, have popular usage as technical terms, and can be screened easily by the person skilled in the art by ordinary methods such as the differential display method focused on each organ as an object.

In addition, Professor Makoto Asashima of Tokyo University, the inventor of this application and an authority of developmental biology, has declared in the attached Declaration: "For practice of the invention, in case a particular organ in a particular vertebrate is targeted, the person skilled in the art can easily (without undue experimentation) determine which gene DNA can be used as stage markers, by ordinary methods such as the differential display method. For researchers in this

field, the opinion 'As to all of amphibians, birds, bony fish, chimaera chondrichthian, mammal, reptile, etc., one skilled in the art could not practice the claimed invention without first carrying out all extensive experimentation.' is unacceptable." As stated above, once vertebrates or organs of vertebrates as study objects are specified, the person skilled in the art can determine gene DNA which can be used as stage markers without undue experimentation, and can culture an organ induced from ectoderm region which has been cut off from the blastula of said animal to the same stage as that of the recipient vertebrate, and can transplant the organ into the recipient of same species by ordinary methods.

The Examiner also states that "[i]n view of the quantity of experimentation necessary to determine the parameters for achieving *in vitro* induced, stage-specific organ preparation, in particular for obtaining organs functioning *in vivo* when transplanted into a recipient of the same species, the lack of guidance provided by the specification as well as the absence of working examples with regard to *any* organ from *any* species of a vertebrate, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention." As in the description of "the basic rule of body formation is common to all the vertebrates and homologous genes are known to have quite a similar function among different species" in the specification, most of the differentiation genes, which function when undifferentiated cells differentiate into particular organs, are common, and a number of these common differentiation genes have been confirmed by the inventors of the present invention (Development, Genes and Evolution, (2000) Vol. 210, p325-327; Biochemical and Biophysical Research Communications, (2000), Vol. 271, p151-157). In fact, Professor Makoto Asashima has declared in the Declaration as follows: "The principle of basic differentiation such as development, cell differentiation, organ differentiation, and so on, is common to all vertebrates, and the same is true of different species." For example, Gurdon et al. (J. Embryols. exp. Morp., 24: 227-48. 1970) teaches the method of constructing clones of Xenopus, and cloned sheep can be obtained by the same method as the method of constructing clones of Xenopus, that is, a method wherein a nucleus obtained from a somatic cell is transplanted into an enucleated egg, and then a clone is produced normally from the egg (Wilmut et al. Nature, Volume 385, 810-813,

February 27, 1997), indicating that the findings as to Xenopus of the present invention can be basically applied to other mammals. Similarly, it is shown in the paper written by the present inventors [see Science (1999, June), Vol. 69, No. 6, p. 529-536] that "Recently, human ES cells (embryonic stem cells) have been constructed, and it is reported that cultured ES cells have differentiated into bones, muscles, epithelial cells or the like after being transplanted into a mouse. ES cells, which are constructed from fertilized eggs or germ cells of embryos, have the ability to differentiate into any cells, tissues and organs, and this ability is common to that of animal cap of amphibian embryos. By using ES cells, study for organogenesis of mammals including human would be greatly advanced."

As mentioned above, although experimental results on Xenopus are described in this specification because of ethical constraints, techniques used in the preparation method of *in vitro* induced organ for transplantation according to the present invention is fully supported with regard to mammals including humans, and it is obvious that the person skilled in the art can practice the present invention based on the information disclosed in the specification without requiring undue experimentation.

Moreover, in the outstanding Office Action, the Examiner himself considers that the present invention can be practiced easily with reference to the paper written by the inventor et al., "Asashima et al. (Proc. Natl. Acad. Sci. USA Vol. 88 pp. 6511-6514, August 1991)", and "Ariizumi et al. (Ariizumi et al. Int. J. Dev. Biol. 35: 407-414 1991)". Applicants respectfully submit that the view that the disclosure in the specification is insufficient is incompatible with this position.

For all of the above reasons, reconsideration and withdrawal of the 35 USC 112, first paragraph rejection are respectfully requested.

Claim 11 (new claim 24) was rejected under 35 USC § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey that the inventors had possession of the invention at the time the application was filed. The Examiner believes claim 11 is too broad considering the evidence in the application, which is limited to Xenopus. This rejection is traversed for the following reasons.

It is the Examiner's position that "Claim 11 recites 'an *in vitro* induced organ for transplantation characterized in that the organ is prepared by the method of *in vitro* induced organ according claim 1.' Given the broadest reasonable interpretation, the claim embraces any organ from any species that is obtained by *in vitro* induction. The claim essentially does not place any limit to the organs claimed. However, the organs taught in the specification are from Xenopus, which are limited to those derived from ectoderm region, and the pronephric tubule is the only one shown to be functioning in the embryo transplantation."

For the same reasons indicated above for claims 1-10, Applicants respectfully disagree. The invention according to new claim 24 does not relate to a particular organ such as a pronephric tubule, but relates to an *in vitro* induced organ for transplantation functioning *in vivo* when transplanted into a recipient vertebrate of the same species, being obtained by culturing an organ induced from ectoderm region which has been cut off from the blastula to the same stage as that of the recipient vertebrate, wherein the stage of the recipient vertebrate is determined by an examination using genome DNA which expresses corresponding to the stage of organs as a molecular marker, and/or by observation of organ tissues. It is clear that target organs should not be limited to organs of Xenopus, which are limited to those derived from ectoderm region, in view of the nature of the present invention. For example, the inventors of the present invention have succeeded in inducing neural tissue, notochord, muscle, pronephros, blood cell, cartilage, pharyngeal epithelium, intestinal epithelium, pancreas, gastric gland and the like from explants of Xenopus by the same method as in the present invention (Moriya, N., Komazaki, S. and Asashima, M., "In vitro organogenesis of pancreas in Xenopus laevis dorsal lips treated with retinoic acid", Develop. Growth Differ. 42, p175-185 2000□Asashima, M., Ariizumi, T. and Malacinski, G.M., "In vitro control of organogenesis and body patterning by activin during early amphibian development", Comparative Biochemistry and Physiology 126, 169-178 2000, Moriya N, Komazaki S, Takahashi S, Yokota C, Asashima M. "In vitro pancreas formation from Xenopus ectoderm treated with activin and retinoic acid." Dev Growth Differ. 42, 593-602 2000). Further, induction of eyeball has been conducted successfully as well (A. Sedohara, A. Fukui, T. Michiue and M. Asashima.," Role of BMP-4 in the inducing ability of the

head organizer in Xenopus laevis", Zoolog. Sci. 19, P67-80 2002), and the induced eyeball has been transplanted to a larva having no eyeballs, and survived there (CLINICAL & EXPERIMENTAL OPHTHALMOLOGY Vol.30 A89 334 2002).

Applicants respectfully submit that they are entitled to the full scope of the present invention, and not limited to the contents of examples and/or embodiments that have been specifically described herein. By way of example, Applicants respectfully point out that US patent No. 4,237,224 (inventors: Stanley Cohen (Stanford University), Herbert Boyer (University of California)) is known as a basic patent as to gene recombination technique, and though the contents of the example of their invention is just an example, claim 1 of the invention is described as follows, and broad scope of the patented claims has been allowed:

"A method for replicating a biologically functional DNA, which comprises:
transforming under transforming conditions compatible unicellular organisms with biologically functional DNA to form transformants; said biologically functional DNA prepared in vitro by the method of:
(a) cleaving a viral or circular plasmid DNA compatible with said unicellular organism to provide a first linear segment having an intact replicon and termini of a predetermined character;
(b) combining said first linear segment with a second linear DNA segment, having at least one intact gene and foreign to said unicellular organism and having termini ligatable to said termini of said first linear segment, wherein at least one of said first and second linear DNA segments has a gene for a phenotypical trait, under joining conditions where the termini of said first and second segments join to provide a functional DNA capable of replication and transcription in said unicellular organism; growing said unicellular organisms under appropriate nutrient conditions; and isolating said transformants from parent unicellular organisms by means of said phenotypical trait imparted by said biologically functional DNA."

With regard to the Cohen- Boyer invention, Applicants respectfully submit that it is clearly improper to think that the invention should be limited to a certain kind of host-vector systems and foreign genes which were specifically exemplified on the grounds that all kinds of host-vector systems and foreign genes were not disclosed in the Cohen-Boyer application. Similarly, Applicants respectfully submit that the present invention should not be limited to particular organs or species, as the principles on which the invention operates are broadly applicable to vertebrate organs and species, as presently recited in the claims. Accordingly,

reconsideration and withdrawal of the rejection are respectfully requested.

Claims 1-3 and 8-17 were rejected under 35 USC § 112, second paragraph, as being indefinite. The claims have been rewritten to recite active method steps, and are believed to be free of this rejection. Favorable consideration of the new claims is respectfully requested.

Claims 12-17 were rejected as being vague and indefinite. Claims 12-17 have been cancelled.

Claim 8 was rejected as reciting an improper Markush group. It is believed that new claim 22 is in proper Markush form.

Claims 1-17 were rejected under 35 USC §§ 102 and 103 as being anticipated or obvious over prior art. To the extent that they may be considered applicable to the presently pending claims, these rejections are traversed for the following reasons.

Claims 1, 2, 10 and 11 are rejected under 35 U.S.C. 102 (e) as being anticipated by Slavkin et al. (US 4,672,032). It is the Examiner's position that Slavkin et al. anticipates the instant claims for the reason that "Slavkin et al. teach a method for in vitro induced formation of dental enamel crystals as restorative material for use in mammals", whereas the specification fails to define the term 'induce' or limiting the term 'stage', and the claims embrace any organ culture in any stage of the ontogeny, including matured organ. Applicants respectfully submit that a dental enamel crystal cannot be considered a "culture of organs", as presently recited in the independent claims; therefore, it cannot form the basis for rejecting the novelty of the pending claims. Accordingly, withdrawal of the rejection is respectfully requested.

Claims 1, 2 and 8-11 were rejected under 35 U.S.C. 102 (e) as being anticipated by Stice et al. (US 2001/0039667). The Examiner believes that Stice et al. anticipate these claims, stating that "Stice et al. teach a method for in vitro induced ungulate embryos and offspring, and teach that the resulting fetuses and embryos may be used for transplantation therapy (see abstract). They go on to teach that the differentiated cells and tissues may be derived from ectoderm (0098, page 8)". It is described in Stice et al. that "the resultant fetuses, embryos or offspring ... may be used as a source of cells or tissue for transplantation therapy for the treatment of diseases such as

Parkinson's disease". Claims 1,2 and claims 8-10 (rewritten as claims 18, 22 -23), which were considered by the Examiner as being anticipated, recite a "preparation method of in vitro induced organ for transplantation". Applicants note that the limitations of claims 3 and 4, which were not rejected on these grounds, have been incorporated into claim 18. It is believed that claims 18, 22 and 23 are free of the rejection. Moreover, claim 24, which replaces claim 11, recites an "in vitro induced organ for transplantation". It is respectfully submitted that the meanings of "in vitro induced organ" and " in vitro induced" in these claims are made clear especially from the description found in page 7, lines 9 to 13 of the present application that "as being non-differentiated cell population, presumptive ectoderm region of the blastula ... without differentiating the tissues when there is no mesoderm inducing activity exists in the culture solution". It means that the organ for transplantation in the present invention is an organ induced by culturing from non-differentiated cells *in vitro*. However, Stice et al. does not induce the organ for transplantation *in vitro*, and thus Stice et al. cannot anticipate the presently pending claims. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 1-6 and 8-11 were rejected under 35 U.S.C. 102 (b) as being anticipated by Asashima et al. (Proc Natl Acad Sci USA 1991 Aug; 88: 6511-14). It was the Examiner's position that Asashima et al. anticipate the instant claims because "Asashima et al. teach in vitro induced organs, such as notochord, muscle, mesenchyme, and epidermis (fig. 2). The organs are induced from early Xenopus (vertebrate) animal-cap cells (ectoderm of a stage 9 blastula), wherein the cell explants are cultured in the presence of activin. Asashima et al. teach that different genes may express at different stages of the embryo development, such as Xar9 (EDF, left column of page 6512)" New claims 18 and 24 (replacing claims 1 and 11) recite an "*in vitro* induced organ for transplantation". The meaning of "*in vitro* induced organ for transplantation" in these claims are made clear especially from the description found in page 7, lines 19 to 28 of the present specification that "*in vitro* induced organs for transplantation need to be cultured up to a certain stage corresponding to the recipients of the same species, that is up to the stage where *in vivo* transplanted organ can function in the living organism". It means that the organ for

transplantation induced from the non-differentiated cells *in vitro* is an organ for transplantation that functions normally *in vivo* of an embryo cultured up to a certain stage corresponding to the stage of the organ. However, Asashima et al. did not transplant organs induced *in vitro* from animal-cap cells (ectoderm of a stage 9 blastula). Even if the induced organs were to be transplanted, it cannot be considered that the transplanted organ will function normally in a recipient embryo. The reason is because, as described in the specification, even if the organ were transplanted in an embryo at a stage different from that of the induced organ, whether the *in vitro* induced organ can function *in vivo* when transplanted in a recipient animal of the same species *in vivo* depends greatly on the period in which it is transplanted. Therefore, it is respectfully submitted that the present invention is not anticipated by Asashima et al.

Further, Asashima et al. teach that different genes may express at different stages of the embryo development, such as Xar9 (EDF, left column of page 6512), however, the point that different genes may express at different stages of the embryo development, such as Xar9, has no relation with the "*in vitro* induced organ for transplantation" of the present invention, and therefore cannot anticipate the presently pending claims. Regarding this point, Professor Asashima, the author of the reference, has declared that "when I wrote these papers, I did not think about transplantation at all. Further, at that time, it would have never occurred to researchers in this field who read this paper that transplantation could be conducted when the developmental stages of recipients and explants are corresponding" (see the Declaration by Professor Asahima, filed herewith, at page 3, line 2). For all of these reasons, it is respectfully requested that this rejection be withdrawn.

Claims 1, 2, 4-6 and 8-11 were rejected under 35 U.S.C. 102 (b) as being anticipated by Ariizumi et al. (Int J Dev Biol 1991; 35: 407-14). The Examiner has taken the position that Ariizumi et al. anticipate the instant claims, stating that "Ariizumi et al. teach in vitro induced organs, such as notochord, muscle, mesenchyme, blood cells, and epidermis. The organs are induced from presumed ectoderm region of Xenopus (see Materials and Methods on page 412), wherein the cell explants are cultured in the presence of activin". To the extent that this rejection

may be considered applicable to the presently pending claims, it is traversed for the following reasons.

New claims 18 and 24 recite an "*in vitro* induced organ for transplantation". The meaning of "*in vitro* induced organ for transplantation" in these claims is made clear especially from the description found in page 7, lines 19 to 28 of the present specification that "*in vitro* induced organs for transplantation need to be cultured up to a certain stage corresponding to the recipients of the same species, that is up to the stage where *in vivo* transplanted organ can function in the living organism". It means that the organ for transplantation induced from the non-differentiated cells *in vitro* is an organ for transplantation that functions normally *in vivo* of an embryo cultured up to a certain stage corresponding to the stage of the organ. However, Ariizumi et al. do not teach anything regarding transplantation of organs induced from explants. Even if the induced organs were to be transplanted, it cannot be considered that the transplanted organ will function normally in a recipient embryo. The reason is because, as described in the specification, even if the organ were transplanted in an embryo at a stage different from that of the induced organ, whether the *in vitro* induced organ can function *in vivo* when transplanted in a recipient animal of the same species *in vivo* depends greatly on the period it is transplanted. Therefore, the present invention is not anticipated by Ariizumi et al. Regarding this point, and as noted above, Professor Asashima, the author of the reference, has declared that "when I wrote these papers, I did not think about transplantation at all. Further, at that time, it would have never occurred to researchers in this field who read this paper that transplantation could be conducted when the developmental stages of recipients and explants are corresponding". For all of these reasons, it is respectfully requested that the rejection be withdrawn.

Claims 1, 2, 4-6 and claims 8-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Asashima et al. (Dev Biol 1990; 198: 330-335, PTO-1449/AG).

It is the Examiner's position that Asashima et al. anticipate 1, 2, 4-6 and 8-11, because "Asashima et al. teach that treatment of amphibian explants with activin A led to differentiation of mesodermal derivatives such as notochord, muscle, mesenchyme, and blood cells (abstract,

figs. 1, 3, table 1)". To the extent that it may be considered applicable to the presently pending claims, this rejection is traversed for the following reasons.

Asashima et al. describe that "recently the mesoderm-inducing effects of the transforming growth factor β (TGF-β) family of proteins have been widely examined. In an attempt to elucidate the functions of these proteins, porcine inhibin A and activin A (erythroid differentiation factor; EDF) were examined. Treatment of explants with activin A led to differentiation of mesodermal derivatives such as mesenchyme, notochord, blood cells and muscle, but inhibin A had a much lesser effect". New claims 18 and 24 recite an "*in vitro* induced organ for transplantation". The meaning of "*in vitro* induced organ for transplantation" in these claims is made clear especially from the description found in page 7, lines 9 to 13 of the present specification that "as being non-differentiated cell population, presumptive ectoderm region of the blastula ... without differentiating the tissues when there is no mesoderm inducing activity exists in the culture solution". It means that the organ for transplantation in the present invention is an organ induced from non-differentiated cells *in vitro*. The meaning of "*in vitro* induced organ for transplantation" in these claims is made clear especially from the description found in description found in page 7, lines 19 to 28 of the present specification that "*in vitro* induced organs for transplantation need to be cultured up to a certain stage corresponding to the recipients of the same species, that is up to the stage where *in vivo* transplanted organ can function in the living organism". It means that the organ for transplantation induced from the non-differentiated cells *in vitro* is an organ for transplantation that functions normally *in vivo* of an embryo cultured up to a certain stage corresponding to the stage of the organ.

However, Asashima et al. teach that treatment of explants in the presence of activin A led to differentiation of notochord, muscle, mesenchyme, blood cells and the like of the explants. This indicates that various kinds of organs can be induced by activin A. Thus, Asashima et al. does not induce organ for transplantation from non-differentiated cells *in vitro*, it cannot be said that it anticipates the present invention. Asashima et al. only teach the differentiation of explants to organs and its relation with activin A. They do not teach induction from non-differentiated

cells to organs for transplantation *in vivo*, nor do they teach the normal function *in vivo* of an embryo cultured up to a certain stage corresponding to the stage of the organ for transplantation. In fact, as noted above, Professor Asashima, the author of the reference, has declared that "when I wrote these papers, I did not think about transplantation at all. Further, at that time, it would have never occurred to researchers in this field who read this paper that transplantation could be conducted when the developmental stages of recipients and explants are corresponding". For all of these reasons, withdrawal of the rejection is respectfully requested.

Claims 1-6 and 8-11 were rejected under 35 U.S.C. 102(b) as being anticipated by Yokota et al. (Biochem Biophy Res Communications 1995 Feb; 207: 1-7) as evidenced by Asashima et al. (Dev Biol 1990; 198: 330-335, PTO-1449/AG). To the extent that it may be considered applicable to the presently pending claims, this rejection is traversed for the following reasons

The Examiner believes that Yokota et al. anticipate to the instant claims, stating that: "Yokota et al. teach that treatment of explants from the animal hemisphere of Xenopus embryos with activin A led to the expression of different genes at different stage (abstract and Discussion). Although, Yokota et al. do not teach which organs the explants would differentiate to, they would have differentiated to notochord, muscle, mesenchyme, and blood cells because it is the intrinsic property of these explants as evidenced by Asashima et al." It is described in Yokota et. al that "The Xenopus homologue of sonic hedgehog (Xhh) was detected in Xenopus embryos at stages 13 and 31 by RT-PCR, but it was not expressed in explants isolated from the animal hemisphere of Xenopus embryos at stage 8-9. Treatment of the animal cap with activin (1-100 ng/ml) induced the expression of Xhh. However, it was not induced by 100 ng/ml basic fibroblast growth factor (bFGF). Whole mount in situ hybridization confirmed the expression of Xhh in the animal cap treated with activin. The expression of Xhh induced by activin was not inhibited in the presence of cycloheximide, suggesting that Xhh is an early response gene induced by activin."

Newly entered claims 18 and 24 recite an "*in vitro* induced organ for transplantation".

The meaning of "*in vitro* induced organ for transplantation" in these claims is made clear especially from the description found in page 7, lines 19 to 28 of the present specification that "*in vitro* induced organs for transplantation need to be cultured up to a certain stage corresponding to the recipients of the same species, that is up to the stage where *in vivo* transplanted organ can function in the living organism". It means that the organ for transplantation induced from the non-differentiated cells *in vitro* is an organ for transplantation that functions normally *in vivo* of an embryo cultured up to a certain stage corresponding to the stage of the organ.

However, Yokota et al. confirmed the expression of different gene at different stage of the explant from the animal hemisphere of Xenopus embyos, treated with activin A by RT-PCR. In other words, Yokota et al. have only confirmed the expression of different gene at different stage of embryo by gene analysis, and have not induced organs *in vitro* from non-differentiated cells, nor prepared organs for transplantation. In addition, even if the explants differentiate to notochord, muscle, mesenchyme and epidermis, as it is taught by Asashima et al., it does not mean that a transplantable organ is prepared from non-differentiated cells. Thus, Yokota et al. do not anticipate the present invention. Withdrawal of the rejection is respectfully requested.

Claims 1, 2, 10 and 11 were rejected under 35 U.S.C. 102 (b) as being anticipated by Agren et al. (Diabetes 1980; 29: 64-69). To the extent that it may be considered applicable to the presently pending claims, this rejection is traversed for the following reasons.

The Examiner has taken the position that Agren et al. anticipate the instant claims, stating that: "Argen et al. teach a method of culturing human fetal pancreas in vitro and these cultivated organs could be used for transplantation in attempts to treat human diabetes." It is described in Agren et al. that: "Human fetal pancreas, obtained at prostaglandin-induced legal abortions, was maintained in organ culture for 6-14 days in medium TCM 199 (5.5 mM glucose) or RPMI 1640 (11.1 mM glucose) supplemented with 20% calf serum and antibiotics." Additionally, it is also stated that "In static incubations of cultured explants there was a poor insulin response to glucose (16.7 mM). By contrast, insulin release was markedly stimulated in the presence of both glucose (16.7 mM) and theophylline (10 mM)." Furthermore, it is stated

that: "The fetal pancreatic material prepared and stored by this means may be used in attempts to cure human diabetes by transplantation." In contrast, new Claims 18 and 24 recite "*in vitro* induced organ for transplantation". It is clear that the term "*in vitro* induced organ for transplantation" in these claims are organs for transplantation induced *in vitro* from non-differentiated cells as it is also clear from the specification (p7, lines 9 to 13) that "As being non-differentiated cell population, presumptive ectoderm region of the blastula.....without differentiating the tissues when there is no mesoderm inducing activity exists in the culture solution."

However, Argen et al. teach that it is possible to culture human fetal pancreas *in vitro* and to use these cultivated organs for transplantation in attempts to treat human diabetes. Human fetal pancreas is not a non-differentiated cell but a differentiated cell, and organs for transplantation are not induced from non-differentiated cells *in vitro*. Thus, Agren et al. do not anticipate the present invention. Accordingly, withdrawal of the rejection is respectfully requested.

Claims 1, 2, 5, 7, 10 and 11 were rejected under 35 U.S.C. 102(b) as being anticipated by Morales et al. (Arch Biochem Biophy). To the extent that it may be considered applicable to the presently pending claims, this rejection is traversed for the following reasons.

The Examiner believes that Morales et al. anticipate the instant claims, stating that: "Morales et al. teach a method of culturing cartilage in vitro in the presence of TGF-β family members and retinoic acid." In Morales et al., it is described that "Retinoids and TGF-β are integral parts of a regulatory network that controls homeostasis, resorption, or growth, depending on their relative contributions." In other words, it teaches a method of culturing cartilage in the presence of TGF-β family members and retinoic acid. New claims 18 and 24 recite an "*in vitro* induced organ for transplantation". It is clear that the term "*in vitro* induced organ for transplantation" in these claims, means that the organs for transplantation induced from non-differentiated cells *in vivo* are organs for transplantation that functions normally *in vivo* in an embryo cultured to a certain stage according to the stage of the said organ, as it is also clear

especially from page 7, lines 19 to 28 of the specification that "*in vitro* induced organs for transplantation need to be cultured up to a certain stage corresponding to the recipients of the same species, that is up to the stage where *in vivo* transplanted organ can function in the living organism."

However, the reference of Morales et al. teach a method of culturing cartilage in the presence of TGF-β family members and retinoic acid. Cartilage is a differentiated cell and not an non-differentiated cell, therefore it does not induce organs for transplantation *in vitro* from non-differentiated cells. Thus, Morales et al. do not anticipate the present invention. For these reasons, withdrawal of the rejection is respectfully requested.

Claims 12-17 were rejected under 35 USC 103(a) as being unpatentable over Hullett et al. (Hum Immunol 1997; 52: 127-37), or Andersen et al. (Acta Ophthalmol 1988; 66: 313-7), in view of Asashima et al. (Proc Natl Acad Sci USA 1991; 88: 6511-14). Claims 12-17 have been cancelled, thereby rendering this rejection moot.

The Examiner indicated that references included in the Information Disclosure Statement have not been considered because they are not in English, and no explanation of their relevance has been provided. Applicants respectfully point out that MPEP 609 III A3 ("Concise explanation of Relevance for Non-English Language Information") states that where the information listed was cited in a search report or other action by a foreign patent office in a counterpart foreign application, the requirement can be satisfied by submitting an English language version of the search report or action which indicates the degree of relevance found by the foreign office. It is respectfully submitted that this requirement was satisfied in the case of the subject references. Accordingly, the Examiner is respectfully requested to make the references of record in the application.

All rejections having been addressed, it is respectfully submitted that this application is in condition for allowance, and Notice to that effect is respectfully requested.

Respectfully submitted,

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